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Mechanisms of arthralgia in targeted therapies for cancer

Mechanismy artralgie při cílené terapii nádorů

Bachelor´s thesis

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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce a ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze 15.5.2017

Podpis:

Abstrakt:
Mnoho protinádorových cílených terapií má za následek neinvazivní bolesti kloubů, artralgii. Mechanismus signalizace bolesti v artralgii není zcela pochopen, ale mnoho studií vede k závěru, že zánětlivé cytokiny hrají důležitou roli v artralgii. Zvláště interleukin (IL)-6 byl detekován ve vysokých hladinách plazmatického séra pacientů léčených terapií anti-vaskulárním endoteliálním růstovým faktorem (anti-VEGF). I když se zdá, že IL-6 je klíčovým faktorem způsobujícím artralgii, byly popsány i další možné mechanismy. Tento článek poskytuje přehled známých informací o vztahu cytokinů a bolesti kloubů. Udává také návrhy možné léčby a budoucího směřování výzkumu léčebných postupů.

Klíčová slova: artralgie, VEGF, cytokiny, IL-6,

Abstract:
Many targeted anti-tumor therapies result in arthralgia, the non-inflammatory joint pain. The mechanism of pain signaling in arthralgia is not entirely understood but many studies lead to a conclusion that inflammatory cytokines play an important role. Especially interleukin (IL)-6 has been detected in high levels in plasma of patients treated with anti-vascular endothelial growth factor (anti-VEGF) therapy. Although IL-6 seems to be the key factor causing arthralgia, other possible mechanisms have been described. This review focuses on the published data about the correlation between cytokines and cancer-related arthralgia. Possible treatments and future directions are also described.

Key words: arthralgia, VEGF, cytokines, IL-6

Abbreviations

25-OHD - 25-hydroxyvitamin D
AI - aromatase inhibitor
BMI - body mass index
Cas9 - CRISPR associated protein 9
ccRCC - clear-cell renal cell carcinoma
CHIKV - Chikungunya virus
CPN - cutaneous polyarteritis nodosa
CRC - colorectal cancer
CRF - cancer related fatigue
CRP - C-reactive protein
CYP19A1-cytochrome P450 family 19 subfamily A member 1
DNA - deoxyribonucleic acid
DRG - dorsal root ganglion
ERK1/2 - extracellular signal–regulated kinase1/2
G-CSF - granulocyte-colony stimulating factor
GM-CSF - granulocyte-macrophage colony-stimulating factor
Gp130 - glycoprotein 130
HFS - hand-foot syndrome
HIF - hypoxia inducible factor
HRE - hypoxic response element
hsCRP - high sensitivity C-reactive protein
IL-10 - interleukin 10
IL-1β - Interleukin 1 beta
IL-4 - interleukin 4
IL-6 - interleukin 6
IL-8 - interleukin 8
JAK - Janus kinase
MAS - macrophage activation syndrome
mTOR - mechanistic target of rapamycin
NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells
NK1R - neurokinin 1 receptor
NRP-1 - neuropilin-1
OA - osteoarthritis
PlGH - placental growth hormone
RA - rheumatoid arthritis
RCC – renal cell carcinoma
siRNA - small interfering ribonucleic acid
SP - substance P
STAT3 - signal transducer and activator of transcription 3
TIE1,2 - tyrosine kinase with immunoglobulin-like and EGF-like domains 1, 2
TNFR1 - tumor necrosis factor receptor 1
TNFR2 - tumor necrosis factor receptor 2
TNF-α - tumor necrosis factor
TRPV1 - transient receptor potential vanilloid 1
VEGF - vascular endothelial growth factor
VEGFR - vascular endothelial growth factor receptor

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1. Introduction

Cancer refers to the large group of diseases caused by abnormal cell growth, division and invasiveness. It is the leading cause of death worldwide. In 2015 cancer took about 8.8 million lives, a number corresponding to one in every six deaths globally. The total of new cancer cases is expected to rise by 70 % in the two upcoming decades. The World Health Organization reported that up to 50 % of cancer cases could have been prevented if current preventative recommendations were followed.

Over the last 50 years, scientists have been intensively trying to find an effective cure; the anti-angiogenic factor therapy belongs to the most successful ones. Even though other new therapies appear to be highly efficient and significantly improve treatment results as well, high-grade toxicity can force patients to retreat from the therapy.

This thesis will deal with the topic of arthralgia and its possible triggers and mechanisms. Arthralgia is a non-inflammatory pain of joints. Many cancer patients suffer from this problem during their cancer treatment. Vascular endothelial growth factor (VEGF) plays a major role in the pathophysiology of joint pain and therefore, anti-VEGF therapies are in particular associated with this complication. VEGF also plays an important role in osteoarthritis (OA). Studies of arthritic processes provide important information on arthralgia associated with anti-VEGF therapy. The important characteristics of OA are the degeneration and breakdown of cartilage in contrast to arthralgia associated with anti-cancer therapies.

The most crucial cytokines involved in arthralgia will be identified and their effects described and compared with inflammatory arthritis. Additionally, this paper will summarize the formation about dysregulation of the mentioned cytokines during the VEGF treatment.

This literature review will compile known information and provide an overview of arthralgia discussing future directions of research and treatment, although there are not many clinical studies presenting clear data about arthralgia and its etiology because of the very complex interaction of immunomodulatory cytokines.

2. Arthralgia

2.1. Definition and incidence

Arthralgia is defined as joint pain, stiffness or aching in the joints. It is an off-target toxicity of therapies targeted at cancer. It has a non-destructive impact on cartilage and articular capsule. Arthralgia can be also described as a joint pain with non-inflammatory condition, unlike arthritis, that is inflammatory (Hardin 1990). In contrast to arthralgia related to cancer treatment, OA results in bone and cartilage degeneration and loss (Maroudas 1976; Bonnet & Walsh 2005; Spector et al. 1997). Arthralgia is undoubtedly one of the most common side effects of anti -VEGF therapy but also occurs

abundantly during aromatase inhibitor treatment, in therapy with certain chemotherapy agents such as taxanes, and during some viral infections. Alasker et al. published a review on toxicities of targeted therapies of metastatic renal cell carcinoma and the prevalence of arthralgia in axitinib treated cohort was 15 %. For sunitinib arthralgia occurred at 11 % of all patients and for sorafenib treatment at 10 % (Alasker et al. 2013). These rates include all grade symptoms (See Figure 1. below).

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint.					

Figure 1. The grading system (1-5) of arthralgia and arthritis according to the Common Terminology Criteria for Adverse Events (CTCAE).
Modified and taken from (CTCAE, 2009).

There are a few researches pointing out the importance of focusing on arthralgia and its cure. A study of women with arthralgia symptoms after inhibitor intake shows, that a severe pain (4 grade of severity) often leads to discontinuation of the treatment before planned time (Chim et al. 2013). Any discontinuation or interrupted treatment increases the mortality rate and worsens the outcome of the therapy (Hershman et al. 2012).

Several cytokines in the pathophysiology of arthralgia have been identified in relation to autoimmune disorders, infections and cancer treatment, including granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 6 (IL-6), interleukin 4 (IL-4), interleukin 10 (IL-10) and Tumor necrosis factor alpha (TNF-α).

2.2. Mediators of arthralgia associated with cancer therapies

2.2.1. Vascular endothelial growth factor

Angiogenesis is defined as the formation of blood vessels from the existing ones. It is a process crucial for development and growth of a tumor larger than $1mm^3$. Bigger tumors lacks enough oxygen and by hypoxia inducible factor (HIF) upregulates production of VEGF, the factor promoting angiogenesis. TNF-α activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which then stimulates production of HIF-α (van Uden et al. 2008). VEGF promotor contains hypoxic response element (HRE) where the HIF-α binds and initiates the transcription of VEGF (Vinores et al. 2006; Riddell et al. 2012).

VEGF is a specific mitogen for endothelial cells. This protein stimulates neovascularization and plays a significant role in angiogenesis (Kelly 2005). Although angiogenesis is a complex process that requires a gradual activation of some tyrosine kinase receptors (e.g. TIE1, TIE2), VEGF is the major rate determining factor of its progression (Jeltsch et al. 2013). VEGF is the signaling molecule for oxygen supply mechanism and it is expressed by many adult organs and various cell types such as macrophages and monocytes (Leung et al. 1989; Berse et al. 1992).

The VEGF family includes VEGF-A, -B, -C, - D, -E, -F and a placental growth factor (PlGH). Their receptors are tyrosine kinases (see Figure 2). The way in which the angiogenetic signal is transduced to the cell depends on the type of the VEGF receptor involved (VEGF-1,-2, 3, NRP-1,-2) (Leung et al. 1989). VEGF family proteins are homodimers except for VEGF-A and PlGH that have been isolated in heterodimeric forms (DiSalvo et al. 1995; Cao et al. 1996).

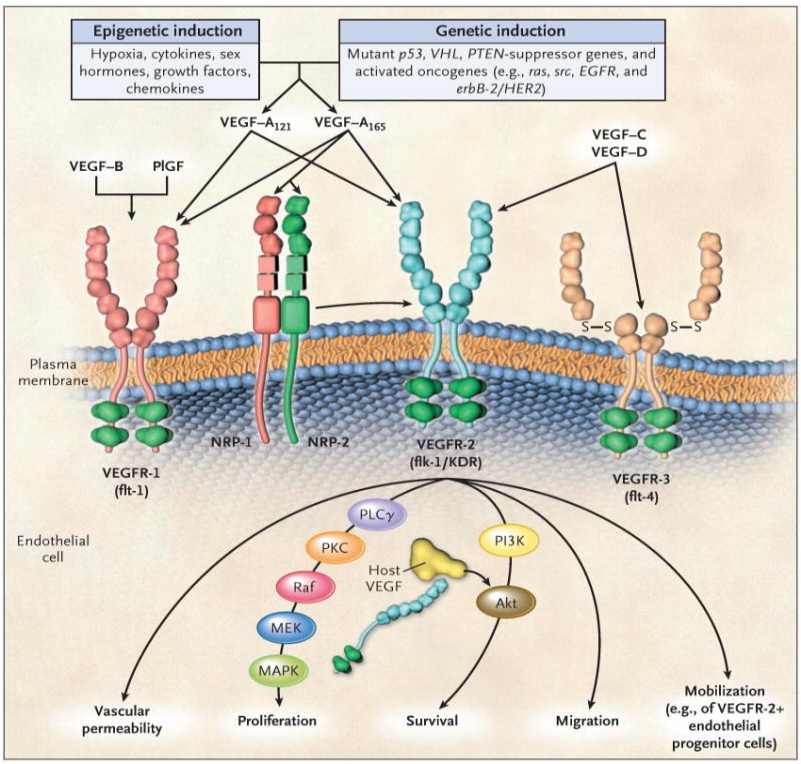

Figure 2. **T**he Family of VEGF Molecules and Receptors Taken from (Kerbel, 2008). Both environmental and genetic factors induce VEGF expression. VEGF-A isoforms are are crucial mediators of tumor angiogenesis and the angiogenic signal is transduced through the VEGF receptor 2.

In the study published by Kim et al., VEGF inhibitors were injected to a rat with an aggressive type of cancer and the growth of tumor decreased rapidly (Kim et al. 1993). The rate of tumor growth was directly proportional to the effect of VEGF inhibition, resulting in greater tumor regression in response to the growth factor inhibition. This study demonstrated that VEGF-induced angiogenesis supports the growth of tumor.

The importance of the VEGF treatment, especially in renal carcinoma, is significant because renal carcinoma is fairly resistant to cytokines (such as interferon-alpha or interleukin 2) and

chemotherapy (Rini et al., 2009). Consequently, many studies were looking into the von Hippel-Lindau (VHL) gene function and its influence on VEGF receptor. VHL is a tumor suppressor located on the short arm of chromosome 3 (3p26–p25). Mutation of the VHL gene is the most common genetic change causing clear-cell renal cell carcinoma (ccRCC). In the sporadic ccRCC the incidence of VHL mutation reaches up to 91 %. The somatic mutations are either missense mutations appearing in 32 % of cases or frameshift and nonsense mutations accounting for 55 % of all mutations (Gossage et al. 2015). The VHL mutation results in the excessive production of VEGF. VEGF not only promotes angiogenesis but also prevents endothelial apoptosis, induces expression of anti-apoptotic proteins in endothelial cells and arrests the development of dendritic cells, promoting tumor growth and allowing it to escape from the immune system (Rini et al. 2011; Cowey & Rathmell 2009). Several studies have suggested that VEGF could be the plasma biomarker of anti-angiogenic cancer treatment. An example of this is an analysis of VEGF levels in patients treated with sunitinib. The levels of VEGF were 2.2 fold higher after 2 weeks of treatment, then fell to the baseline values and repeatedly increased with the subsequent cycles (Norden-Zfoni et al. 2007). Nevertheless, evaluation of VEGF levels has never been validated for use in clinical practice.

Aside from its role in angiogenesis, VEGF is also neuropathic factor stimulating the growth of dorsal root ganglion (DRG) axons (Sondell et al. 2000). Pelletier et al. explain, the neurotropic ability of VEGF in their study (Pelletier et al. 2015). New blood vessels can support the creation of new nerves and then the inflammation in a synovial joint causes pressure, which leads to a development of painful sensation through them. The innervation angiogenesis brings new nerves to aneural cartilage and that will also cause pain during movement. The innervation of the cartilage and neovascularization is the main cause of pain in OA and therefore anti-VEGF antibodies are the best candidates for the therapy targeting this disorder. Some researchers have proposed that this mechanism could also contribute to arthralgia. It has been reported that treatment with antibody against VEGF is beneficial for patients with osteochondral defects. Inhibiting the activity of this growth factor contributed to the cartilage repair (Nagai et al. 2014).

Interestingly, cartilage damage in OA is not always associated with joint pain and the severity of OA does not correlate with the intensity of pain (Davis et al. 1992). Cartilage is an aneural tissue and cannot transduce pain. Normal joint nociceptors have a high threshold for pain so that the everyday movements do not hurt. Some scientists believe that if the damage does not determine the pain grade then it also does not cause pain by itself. Rather, the pain is mediated by inflammatory cytokines and the same cytokines can activated pain pathway in the absence of cartilage damage, causing arthralgia (Dieppe & Lohmander 2005). In a study on OA patients treated with hyaluronic acid and dermatan sulphate it was shown that the joint pain was attenuated by the oral medication and cytokine levels changed correspondingly. Final concentrations were observed to decrease compared to the control group. IL-6, IL-10, TNF-α and GM-CSF levels declined together with the symptoms

supporting the theory that these proteins play a role in thee transduction of joint pain (Nelson et al. 2015).

The anti-angiogenic inhibitors bind to the VEGFs and block them from binding to their receptors, preventing formation of new blood vessel and enabling cartilage repair (Nagai et al. 2008). Bevacizumab as explained by a study Nagai et al., binds to VEGF but does not change or inhibit its expression and the concentration of VEGF measured in the synovium fluid remained stable in a study of OA patients (Nagai et al. 2014).

Although VEGF plays a role in cartilage damage in inflammatory arthropathies, in certain situations joint pain can be induced by anti-VEGF or anti-vascular endothelial growth factor receptor (VEGFR) treatment (Langenberg et al. 2011; Garcia et al. 2008). When VEGF-A isoforms bind to VEGFR2, this receptor directly promotes nociception of neurons (Hulse et al. 2014). DRG neurons express VEGFR2 and its inhibition sensitizes the neurons. Also, VEGF-A_{165}b isoform is known to be neuroprotective, hence anti-VEGF therapy might block the neuroprotective properties and cause neuropathic pain (Verheyen et al. 2012; Verheyen et al. 2013; Beazley-Long et al. 2013). The balance between isoforms appears to be important and Hulse et al. clarify this, with results of a study on mice. High concentration of VEGF-A_{165}a isoform in the microenvironment of sensory neurons intensifies pain perception through VEGFR2. Five minutes after detected action potential in the peripheral neurons with administrated VEGF-A_{165}a, the neurons had lowered activation threshold and became sensitive to mechanical stimuli. The isoform b attenuates the effects of isoform a, therefore, the isoform VEGF-A_{165}b is a promising molecule for applications in analgesic therapy (Hulse et al. 2014).

A relationship between VEGF and IL-6, another key mediator of arthralgia, has been suggested. Anti VEGF therapy combined with anti-IL-6 therapy is key to abrogate proliferation of cancer cells and invasion of residual cancer cells into the rest of the body. Due to the fact that VEGF synthetized by the glioblastoma cells induced IL-6 and the IL-6 upregulated VEGF using STAT3 factor activation, both proteins pathways overlap and are essential for the tumor growth. The combined knock-down of both pathways resulted in lowered or almost completely inhibited synthesis of VEGF and IL-6 proteins (Angelo & Kurzrock, 2007; Saidi et al., 2009).

2.2.2. C-reactive protein

The study of Limper et al. demonstrated that patients suffering from arthralgia have activated acute-phase response to some extent because they have higher hsCRP levels compared to healthy controls. In the cases where arthralgia progressed into arthritis, the amount of IL-6 and IL-10 cytokine escalated (Limper et al. 2012). These results suggest that CRP can be a part in a signaling pathway leading to arthralgia.

It is widely known that CRP represents an immune response of a body to the tumor growth. High levels were reported especially in colorectal carcinoma cohort (Groblewska et al. 2008). CRP

can stimulate production of some cytokines like TNF-α, IL-6 and vice versa (Castell et al. 1990). Decreasing levels of CRP usually coincide with improvement of arthralgia (Thummala et al. 2015).

2.2.3. Tumor necrosis factor-alpha

The regulation of immune cells and inflammation in the body is largely mediated by a factor TNF-α. As it includes the whole immune system, TNF-α must be produced by many cell types within the body. Macrophages are the major site of TNF- α expression and in reaction to tumor cells, TNF- α is released from the Golgi complex (Shurety et al. 2000). Both "pro" and "anti" tumor activity were described in TNF-α (Balkwill 2006). It can induce apoptosis and inflammatory mediators by binding to tumor necrosis factor receptor 1 (TNFR1) (Varfolomeev & Ashkenazi 2004). Tumors and their microenvironment can produce this cytokine in low and high amounts respectively (Li et al. 2009; Carswell et al. 1975).

Anti-TNF agents such as the chimeric monoclonal antibody infliximab are commonly used in targeted therapies for autoimmune diseases. Many scientists assumed that the alleviation of arthralgia during the course of anti-TNF therapy was caused by the suppression of inflammation. Boettger et al. brought a new perspective by testing whether the inhibition of TNF-α has a direct effect on neurons. The results proved to be right. The mechanical hyperalgesia faded but the inflammation of joint persisted (Boettger et al. 2008).

TNF-α can act directly on nociceptors and change the receptor potential to elicit transduction of pain signal. The depolarization of peripheral terminals can be achieved by regulation of ion channels. TNF-α affects its receptors TNFR1 and TNFR2 but the pain behavior seems to be dependent on activation of only one subtype, the TNFR1 that is expressed by sensory neurons. In a mice model study, the knockout of TNFR2 did not reduce hyperalgesia (Sommer et al. 1998).

Deswal et al. found out, that lower levels of estrogen in the postmenopausal women increase the cytokine (TNF-α, IL-6, IL-1) secretion (Bismar et al. 1995; Deswal et al. 2001). The production of TNF-α also depends on BMI and on the amount of adipose tissue in the body (Hotamisligil et al. 1995).

Lastly, TNF-α induces the expression of transient receptor potential vanilloid 1(TRPV1) gene through factor-κB and hypoxia-inducible factor. That might also be a contribution to pain signaling through DRG neurons (Hatano et al. 2012).

Corticosteroids are frequently used in the treatment of arthralgia related to systemic inflammatory conditions. They inhibit certain cytokines including TNF-α, thus suggesting that TNF-α could participate in arthralgia aggravation (Lovato et al. 2016).

2.2.4. GM-CSF

GM-CSF stimulates maturation and proliferation of macrophages, which secrete other cytokines. Chow et al. suggested a possible arthralgia etiology associated with the disease caused by

Chikungunya virus (CHIKV). 60 % of the CHIKV cohort had increased levels of GM-CF (Chow et al. 2011). The other high cytokine levels observed were IL-6, IL-4, IL-10 and TNF-α suggesting that cooperation of more cytokines lead to long-lasting and reoccurring arthralgia after the onset of the virus infection (Chirathaworn et al. 2013; Santiago et al. 2015; Tappe et al. 2017).

Schiller et al. reported 24 % incidence or arthralgias and myalgias during the study of 3-hour paclitaxel infusion delivered to patients with untreatable malignancies. The paclitaxel administration was divided into "with" and "without" granulocyte-colony stimulating factor (G-CSF). Authors of this study suggest that the augmentation of arthralgia and myalgia toxicity is related to infusion with G-CSF because it appeared after the infusion. Particularly the arthralgias repeatedly occurred 1 or 2 days after drug administration and ceased within 6 days (Schiller et al. 2017).

2.2.5. Substance P

Another molecule of interest is substance P (SP), a neurotransmitter that is upregulated in some cancers, including colorectal cancer (CRC). This highly expressed mediator, was identified in retinaculum, fat pad, periosteum, and subchondral plate and these findings were also associated with increased expression of its receptor NK1R (Wojtys et al. 1990). A recent article written by Chen et al. maintains that the CRC promotes greater secretion of SP which acts as a marker for the cancer progression. Elevated amount of SP occurred in 68,5 % of patients. Increased concentration correlated with poorer outcome and worse survival rate (Chen et al. 2016). The naturally occurring ingredient of chili pepper, capsaicin, activates its receptor TRPV1 by binding to it and causes substance P depletion from sensory neurons (Jessell et al. 1978). The activation also leads to calcium influx that results in a release of certain neuropeptides. This whole release process affects epithelial and immune cells and causes them to produce for example IL-6 and TNF-α (Holzer 1988). In 2011 an article emerged proposing a theory that mitigated pain could be a result of neuronal loss of function (Anand & Bley 2011). In the naturally occurring situation, TRPV1 can cause temporary depolarization after being activated through heat, acidosis or antagonists. By binding an exogenous agonist such as capsaicin, that is chemically a stable molecule, the effects becomes permanent and the neuronal endings collapse because of calcium overload and loss of membrane potential in mitochondria. After repeated application of capsaicin the neurons became nearly immune against mechanical and thermal stimulation (Nolano et al. 1999).

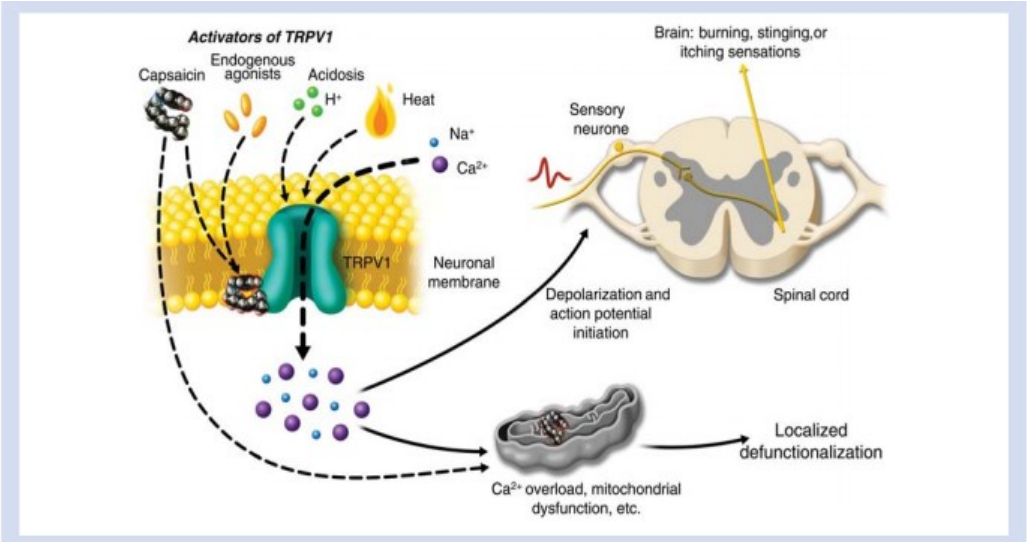

Figure 3. Simplified mechanism of capsaicin induced pain and defunctionalization. Taken from (Anand & Bley 2011).

2.2.6. Vitamin D

Studies on postmenopausal women treated with aromatase-inhibitor (AI) for breast cancer state that arthralgia correlates with measured amount of 25-hydroxyvitamin D (25-OHD). Although the results have not been unambiguous, several studies have reported a correlation between vitamin D levels and arthralgia. Insufficient amount or deficiency of 25-OHD (less than 10 ng/ml) caused arthralgia in 34,7 % of the patients. Much lower proportion of non-destructive and non-inflammatory pain (15 %) was identified within the cohort with 25-OHD level above 30 ng/ml. Later, with rising level of 25-OHD in the serum, the intensity of pain decreased. The authors of this study concluded that arthralgia is undoubtedly related to vitamin D levels (Heidari et al. 2013). The severity of pain was associated with 25-OHD deficiency because the lowest levels presented the highest severity of arthralgia (Servitja et al. 2015).

Garcia-Giralt et al. analyzed results of women treated with AI between the years 2006-2012, where approximately half of the patients reported worsening of arthralgia. CYP17A1, CYP27B1, and VDR genes were identified to have strong association with arthralgia (Garcia-Giralt et al. 2013). Genetic variants of these genes, that enable vitamin D activation, exhibit risk of AI-related arthralgia. Furthermore, future determination of specific single nucleotide polymorphisms within the mentioned genes could be highly beneficial for prevention of arthralgia and assessing the most convenient treatment of postmenopausal breast cancer patients.

2.2.7. IL-6

IL-6 is a pleiotropic cytokine that was first recognized as a factor inducing a production of immunoglobulins by B lymphocytes. Later it was discovered that it is also one of the myokines produced by myocytes in a reaction to muscle contractions (Pedersen & Febbraio 2008). It also causes cells such as T-cells or plasmacytoma and myeloma cells to proliferate and differentiate. IL-6 enables the pheochromocytoma PC12 cells to differentiate into neuronal cells and in rats it stimulates the

release of hormones such as prolactin or luteinizing and growth hormone (Umeguki et al. 1996; Taga, Tetsuya 1997). Although IL-6 is characterized as a pro-inflammatory cytokine, there have been numerous studies published reporting on the evidence of its anti-inflammatory effects.

With the induction of tocilizumab (IL-6 receptor inhibitor) the level of IL-6 increases and researchers suggest that the increase may affect the development of non-inflammatory joint pain. After the first administered dose of tocilizumab antibody, 36,7 % of all patients developed arthralgia of large joints and the level of IL-6 rose significantly compared to healthy controls without arthralgia. The 29 subjects suffering from large joint pains were in the cohort with rheumatoid arthritis (RA). The newly developed pain started a day after tocilizumab injection and usually lasted for a week. It originated in different joints than the ones affected by RA and there were no other signs of RA (Uda & Saiki 2013).

Increased levels of IL-6 are thought to cause arthralgia in some viral diseases. Levels of cytokines in serum of patients with Chikungunya fever caused by the CHIKV were monitored and especially IL-6 and IL-8 were abnormally higher. In patients reporting persistent joint pain2-3 months after the onset of the illness, the concentration of IL-6 in the serum was much higher compared to patients with no persistent arthralgia (Chow et al. 2011).

Another Japanese study provided data that show how IL-6 influences patient's inflammatory conditions, in this case, patients with cutaneous polyarteritis nodosa (CPN). Out of 45 subjects observed and examined nineteen people, 42,2 % had elevated IL-6 levels in the blood serum. More importantly, 32 people suffered from arthralgia (71,1 %) and from the group of patients with elevated IL-6, 94,7 % experienced arthralgia. CRP and TNF-α concentrations were also elevated. In the group of subjects with normal levels of IL-6 in the serum, arthralgia occurred only in 53,8 % of the cases. Overall, the incidence of non-inflammatory joint pain was higher in the group of people with higher IL-6 levels (Kawakami et al. 2012).

Apart from all the attempts to detect the link between arthralgia and specific cytokine, some studies on rats already focus on the possible ways of how certain interleukins cause and promote the joint pain or pain in general. IL-6 receptor family all comprise glycoprotein 130 (gp130) and this common feature is found in all DRG neurons. Segond von Banchet et al. suggest DGR neurons express the IL-6 receptor (Segond von Banchet et al. 2005). Gp130 is a main transducing unit in the receptor signaling, possibly pain signaling, to neurons. Long-term exposure to IL-6 led to increase number of neurons that were able to react to substance P by enhancing the expression of neurokinin 1 receptor (NK1R) that is activated by the substance P. On top of that, several published studies state that IL-6 promotes mechanical hypersensitivity and heat hypersensitivity (Obreja et al. 2002; Quarta et al. 2011).

Brenn et al. suggested specific IL-6 pain signaling in group C nerve fibers. Firstly, the injection of IL-6 and its soluble receptor evoked rapid sensitization. The co-administration of soluble gp130, that neutralizes IL-6, prevented C-fibers sensitization. These results also depended on the dose of injected IL-6. Low concentration of IL-6 in the joint had no or very little effect (Brenn et al. 2007).

To summarize all the results from the mentioned studies, IL-6 is a key cytokine for arthralgia. Its role is very important because it can elicit non-inflammatory joint pain even without combining the effects of other suspected cytokines like TNF-α or IL-4 (Siebert et al. 2007). This cytokine has been mainly known for causing inflammatory pain, but all collected evidence is proving that IL-6 exerts either direct effect or influences the signaling cascade leading to arthralgia. In addition, IL-6 can act as a predictive biomarker for metastatic renal cell carcinoma (Negrier et al. 2004). Overall survival as well as the progression free survival is worsened by the elevated IL-6 in serum after the bevacizumab chemotherapy (Hara et al. 2017).

2.2.8. IL-10

IL-10 was first described in the 1989 as a factor inhibiting production of T helper 1 (Th1) cells cytokines (Fiorentino et al. 1989). This immunomodulatory cytokine is produced not only by monocytes and lymphocytes, but also by tumor cells such as colon carcinoma, renal cell carcinoma and neuroblastoma cells (Gastl et al. 1993). As the research from Terai et al. explains, IL-10 is produced by melanoma cells as well, but only in the presence of IL-6 in the medium. The exact mechanism remains unclear but the obtained data lead to the conclusion that blocking the JAK signaling pathway (inhibition of STAT3 or ERK1/2 phosphorylation) represses the production of IL-10, therefore, it increases the tumor resistance against therapy (Terai et al. 2012).

IL-10 is able to activate macrophages that would induce tumor angiogenesis. The polarization of macrophage in the presence of IL-4 and IL-10 cytokine enhances production of IL-10 in high concentrations. The macrophages stimulated this way will, later on, become pro-angiogenic and the ones without IL-10 will inhibit the creation of new vessels (Dace et al. 2008; Apte et al. 2006).

2.2.9. IL-4

This pleiotropic cytokine stimulates activation and differentiation of B cells, initiates differentiation of T cells and acts on many other cell types. Macrophages are alternatively activated by IL-4. IL-4 is upregulated in many cancer types and can also induce proliferation, growth or reoccurrence of cancer (Chang et al. 2015; Roca et al. 2012; Prokopchuk et al. 2005). IL-4 receptor (IL-4R) blockade inhibits metastasis in some types of cancer (Hosoyama et al. 2011).

IL-4, when used as experimental therapy in cancer patients, is well tolerated and significantly reduces production of inflammatory cytokines (Maher et al. 1991). The occurrence of arthralgia, as a side effect, was observed in 21 % of patients in a study on efficacy of the administrated IL-4 to chronic lymphocytic leukemia cohort. Together with fatigue, arthralgia seems to be dose related in regard to the more frequent presence at higher doses of IL-4 (Lundin et al. 2001).

3. Antineoplastic therapies associated with arthralgia

3.1. Anti-VEGF agents

Anti-VEGF therapy targets VEGF or its receptor, blocking angiogenesis and tumor growth. Many anti-VEGF medications have good efficacy in treatment of primary tumors. On the other hand, some cases reported reduced survival and accelerated metastasis (Ebos et al. 2009).

3.1.1. Monoclonal antibodies

As already mentioned, Bevacizumab (trade name Avastin) is a monoclonal antibody best known for its anti-angiogenic properties. It has been approved for the use in European Union since 2005 and metastatic colon cancer is one of the most frequently bevacizumab-treated cancers (EPAR ,2009).

Some of the conducted studies on this medication show results that clearly prove that combination of chemotherapy with bevacizumab enhances the effect of the treatment. The levels of IL-6 drastically decreased compared to patients receiving chemotherapy alone already after the first round of bevacizumab administration. It also increased the T-cell counts in peripheral blood. This treatment prolongs the progression free time and rises survival rates in metastatic melanoma cohort (Mansfield et al. 2013).

3.1.2. Antibody derivates

Antibody derivates include drugs such as ranibizumab which is a fragment developed from Bevacizumab often used for treating macular degeneration. Some articles doubt the cost-effectiveness of the derivate and suggest replacing the treatment with Bevacizumab instead (Stein et al. 2014).

Aflibercept is also known under the name VEGF-trap and is one of the drugs used to treat metastatic colorectal cancer. It is a recombinant fusion protein comprising three domains from VEGFR1and a constant portion of human immunoglobulin G. Aflibercept treatment causes all grade toxicities and some of them are thought to correlate with increases of IL-6 and IL-10 (Shonka et al. 2013).

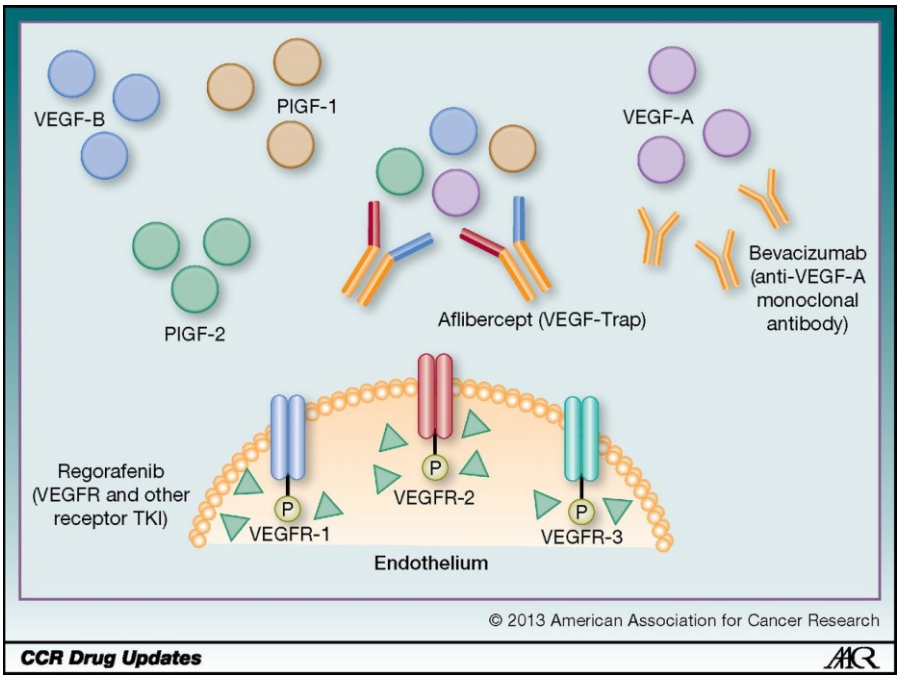

Figure 4.The inhibition mechanism of tegorafenib, aflibercept and bevacizumab. Taken from (Ciombor et al. 2013).

3.1.3. Orally-available tyrosine kinase inhibitors

For example very frequently used sunitinib, pazopanib, lapatinib, sorafenib, axitinib belong to this category.

Sunitinib is widely used for treating metastatic renal cell carcinoma (RCC). Treatment by this medication can elevate the levels of IL-6 by more than 100 % (Motzer et al. 2007). Porta et al. observed this elevation in 37,3 % of patients in the sunitinib efficacy study (Porta et al. 2013). Harmon et al. provide proof not only for the reduction of tumor growth, but also suggest for the prediction value of low levels of VEGF receptor 3, which can be used as a biomarker for outcome of sunitinib treatment (Harmon et al. 2014).

Another kinase inhibitor drug sorafenib is known to cause arthralgia to the treated patients (Guidetti et al. 2014). The treatment also causes enhancement of IL-4 and IL-6 levels detected in the plasma. 44 % of patients with metastatic renal cell carcinoma had these concentrations elevated (Zurita et al. 2012).

3.1.4. Adverse effects of anti-VEGF therapy

Anti-VEGF therapy may be administered using diverse group of antibodies such as sunitinib, sorafenib, pazopanib, bevacizumab, paclitaxel and aflibercept. As VEGF inhibitors, these antibodies are used to stop or slow down angiogenesis and neovascularization. Many side effects and toxicities appear after treatment with currently available antibodies, but the severity varies. The severity can be resolved by lowering the dosage, postponing or even interrupting the treatment. Interrupted treatment as well as some of the common toxicities also lead to higher risk of death (Schmidinger 2013).

The side effects of the VEGF-inhibitor treatment can be divided into following: general symptoms, cardiovascular toxicities, skin toxicities, gastrointestinal symptoms and arthralgia (Schmidinger 2013).

Cancer-related fatigue (CRF) is the most common toxicity caused most frequently by sunitinib. Especially in breast cancer, patients experience CRF even years after successful treatment. Newest research suggests prescribing supervised exercise that significantly reduces this side effect (Meneses-echávez et al. 2015). Arthralgia and CRF are usually appearing together during chemotherapy. These symptoms are strongly related and both correlate with CRP and vitamin D–binding protein levels in patients (Bauml et al. 2015)

The complete mechanism of fatigue is not known yet but a few hypotheses already exist and due to the severity of the side-effect and its affect on patient´s lives there are a lot of studies in progress to solve this issue. There have been investigations going on since the1990s focusing on the inflammation hypothesis indicating that IL-1β and TNF-α promote fatigue by sending signals to the brain from peripheral immune system (Meyers et al. 2005). Certain psychological factors such as stress and biological factors including modulation by pro-inflammatory cytokines and inflammation participate in the CRF mechanism (Bower 2014). The changes in IL-6 during chemotherapy might also have an impact on the CRF (Liu et al. 2012).

Other reported toxicities listed as “general symptoms” are asthenia, weight loss or myalgia and depression. Hemorrhage has also been associated with the usage of VEGF inhibitors. As VEGF inhibitors (VEGFI) interrupt the signaling function of this endothelial factor, it interferes with fast and effective healing of wounds and also restricts capillaries renewal, therefore causing bleedings (Scappaticci et al. 2005; Schmidinger 2013). All these general symptoms are interconnected and may aggravate each other.

High arterial pressure is one of the most common side effects that appear after introducing the anti-VEGF therapy and many clinical trials reported high occurrence of hypertension in treated patients (Mittal et al. 2014; Girardi et al. 2010). Hypertension, as well as some other treatment-related adverse events (palmar-plantar erythrodysesthesia and general symptoms) were noticed mainly after the sunitinib usage, but none of it reached 4 grade of severity in research (Motzer et al. 2009).

Cellular nitric oxide is a pulmonary vasodilator and blocked VEGFR2 reduces the release of the oxide in arterial smooth muscle cells therefore it is a possible cause for arterial hypertension during cancer treatment (Tang et al. 2004; Fan et al. 2014).

Left ventricular dysfunction is another quite frequently occurring type of cardiotoxicity and it is caused by tyrosine-kinase inhibitors as well as monoclonal antibodies (Yeh & Bickford 2009; Bordun et al. 2015).

The occurrence of thromboembolic effect was increased after anti-VEGF treatment, especially after Bevacizumab (anti-VEGF monoclonal antibody), sorafenib and sunitinib (tyrosine kinase inhibitors) application. Researchers proved that using bevacizumab combined with chemotherapy

increases the incidence of arterial thromboembolism by 2,1 % (Scappaticci et al. 2007). There are many pathways leading to thrombotic event but anti-VEGF treatment removes the essential component of maintaining homeostasis and dealing with coagulation cascade (Shord et al. 2009).

The most reported arterial thrombotic events associated with cancer treatment by anti-angiogenic treatment are cerebrovascular accidents and myocardial infarction. Although the incidence is 1% it can become lethal for diabetic patients who are at high risk for cardiovascular complications (Coutinho et al. 1999). According to the analyzed data from 1950 to 2012, VEGF inhibitors increase the likelihood of arterial thrombotic events (Faruque et al. 2014). Nalluri et al. meta-analysis shows data claiming that the incidence of venous thrombotic events can rise up to 19 % (Nalluri et al. 2015).

These events include deep venous thrombosis, pulmonary embolism, mesenteric venous thrombosis, and axillary venous thrombosis (Faruque et al. 2014; Thulliez et al. 2014).

Palmar-plantar erythrodysesthesia, also called the hand-foot syndrome (HFS) is one of the most common side effects of the sunitinib treatment together with others like hypertension, fatigue, and diarrhea. In the research comparing sunitinib and interferon alpha (IFN-α), these toxicities developed more in the sunitinib cohort but did not reach grade 4 of severity (Motzer et al. 2009). According to Columbia et al. the incidence of HFS in sunitinib studies is 30 % (Columbia et al. 2011). Endothelial repair and survival abilities are impaired by the treatment and highly-pressured areas on soles and palms lack the competency to repair in time, therefore, remain damaged until reaching the common HFS characteristics.

Hair or skin depigmentation, dry skin, alopecia and rash can also occur during the anti-VEGF treatment but not many researchers determined the direct link between the treatment and the toxicity (Schmidinger 2013). Some skin toxicities such as acneiform of skin rash develop in 90 % of patients receiving cetuximab and panitumumab medications (Saif et al. 2008).

As the anti-VEGF treatment suppresses angiogenesis and neovascularization, the inadequate blood supply results in weakening the walls of bowel. The gastrointestinal tract cannot hold the pressure of incoming food and perforates. Another research proposed that perforation can occur after bowel damage with disabled wound healing (Han & Monk 2007). The risk of bowel perforation is very low (up to 1,5 %) and depends mostly on the type of cancer but it is the most lethal (21,7 %) side effect among the mentioned ones (Hapani et al. 2009; Shord et al. 2009; Hainsworth et al. 2004).

3.2. mTOR inhibitors

Everolimus is a derivate of rapamycin blocking mechanistic target of rapamycin (mTOR) kinase. It has antiproliferative effect on some type of cancers. Everolimus is also used for immunosuppression after transplantations. The treatment-induced arthralgia is resolved by reduction of inhibitor dosage (Iaria et al. 2006).

3.3. Microtubule inhibitors

Paclitaxel (trade name Taxol) is a drug targeting tubulin in the cell. It belongs to taxane medication group which causes up to 90 % of neuropathy cases (including arthralgia) among the taxane treated patients (Imai et al. 2012). Ripamonti et al. found out that pathologies such as myalgia and arthralgia have prevalence of up to 20% in Taxol treated patients (Ripamonti et al. 2014). Paclitaxel treatment increases plasma levels of IL-6 and IL-10, but this increase is schedule-dependent. The same study explains that IL-10 levels strongly correlated with joint pain reported by the patients and their weekly doses of paclitaxel (Pusztai et al. 2004).

3.4. Aromatase inhibitor

Arthralgia and joint stiffness are very common toxicities for breast cancer survivors and can last many years after the disease onset. The etiology of arthralgia in breast cancer is thought to be related to abrogation of estrogen synthesis or function which is commonly employed as a part of treatment of hormone-positive breast cancer. Crew et al. reported a 50 % incidence of arthralgia among postmenopausal women receiving aromatase inhibitor (AI) treatment for breast cancer (Crew et al. 2007). Considering the fact that breast cancer is one of the leading causes of deaths among women, arthralgia influences the quality of life of a large part of the population (Parkin et al. 2005). The relation between arthralgia and AI cancer treatment is still unknown but some analyses confirm the correlation with low levels and level drops of estrogen usually observed in perimenopausal women (Ho et al. 1999). Surprisingly the linkage between estrogen levels and arthralgia was discovered already in 1925 (Cecil & Archer 1925). Estrogen depletion could be the cause of higher sensitization of nociceptors in the joint, however this theory has not been proven and only few researches support it (Dawson-basoa & Gintzler 1993). Moreover, according to some researches, the levels of certain cytokines such as IL-6 and TNF-α are increased by diminishing estrogen (Rachon et al. 2002; Zheng et al. 1997).

Aromatase, coded by CYP19A1 gene, is an enzyme synthetizing estrogen. The mechanism of aromatase inhibition therapy is based on inhibition of the last step of biosynthesis when the enzyme is converting androstenedione to estrone and testosterone to estradion (Bulun et al. 2004). Further research detected 8 alleged polymorphism in the CYP19A1 gene lowering the risk of arthralgia. On the other hand, the haplotype M_3_5 of CYP19A1 gene is increases that risk (Mao et al. 2011; Park et al. 2011). Although there is a limited number of articles focused on this specific topic and Garcia-Giralt et al. did not manage to prove this theory in their own study (only associated SNP rs4775936 with worsening pain), all results should be considered because they might match with future research and play pivotal role in understanding the exact mechanism of joint pain (Garcia-Giralt et al. 2013).

Several tissues produce estrogen but the most important source in postmenopausal woman is the adipose tissue due to the decrease in the ovarian production. Therefore, it has been hypothesized that the body weight could be also a factor influencing the severity of arthralgia. Folkerd et al. provide

supporting evidence for this theory. Body mass index (BMI) affects the estrone and estradiol levels in human body (Folkerd et al. 2012). Higher levels were detected with higher BMI making aromatase inhibition treatment less effective (Decker et al. 2014). The estrogen resides more in the secondary tissues producing estrogen therefore the aromatase inhibition appears to be less effective. Five out of eight studies in a systematic review of Ioannides et al., presented that higher BMI resulted in worse breast cancer outcome (Ioannides et al. 2014). Thus, weight reduction could not only lead to amelioration of arthralgia but also to improvement in cancer survival in hormone-positive breast cancer patients.

4. Emerging treatments for arthralgia associated with cancer treatment

Due to the fact that the mechanism of arthralgia has not yet been fully clarified, there are only a few studies and clinical trials describing a treatment that reduces joint pain. Bee venom from species *Apis mellifera* was used for acupuncture on rats with induced spinal cord injury. The damaged tissue expressed high levels of pro-inflammatory cytokines such as IL-6 and TNF-α. After the injection of venom to the acupoints the IL-6 levels dropped (Nascimento de Souza et al. 2017). Also, a Chinese study detected the same cytokine levels decrease after warm acupuncture treatment (Cai et al. 2014). There are more cases of recent trials of acupuncture that lowered the concentration of IL-6, TNF-α (Wang et al. 2016). All these studies have similar results that include the decline in cytokine concentrations. In addition, Chen et al. confirmed that the acupuncture has positive effects on AI-induced arthralgia (Chen et al. 2017). These novel results, however, need to be verified in further clinical trials.

TRPV1 is a capsaicin-sensitive ion-channel that gives a rise to pain. Gp130 is important for TRPV1 expression and transmission of pain signals. An experiment on mice with gp130 knock-out showed that the mice were less sensitive to mechanical stimuli and the expression of TRPV1 was much lower in the DRG neurons compared to control mice (Malsch et al. 2014). Gp130 is an IL-6 family receptor subunit that also plays an important role in maintaining hypersensitivity to mechanical stimuli (Quarta et al. 2011). Theoretically, blocking this receptor would preclude arthralgia development despite the high levels in the plasma serum. Tocilizumab and siltuximab are already used anti-IL-6 targeted medications but the available literature on their use for arthralgia is still limited (Baldo 2016; Deroux et al. 2016). The effects of these drugs seem to be based on the suppression of the macrophage activation syndrome (MAS). The central factor seems to be IL-10. The suppression of IL-10 leads to a dysregulation of the cytokine net and creation of the "cytokine storm" (Schulert & Grom 2014; Behrens et al. 2011).

In addition, tocilizumab was successfully used in a treatment for multicentric Castleman's disease (Castleman & Towne 1954). The overproduction of IL-6 plays a key role in the

pathophysiology of this rare disorder. After 8 weeks of treatment, the joint pain subsided together with other symptoms (Oshima et al. 2017).

Currently, there is not enough information on how to interconnect all the cytokines into one pathological model. Hence, it is unclear how to select patients for anti-IL-6 therapy.

5. Conclusion

IL-6, IL-10, TNF-α, GM-CSF and many other inflammatory cytokines appear at high concentrations in peripheral blood of cancer patients with induced targeted chemotherapy. The complex interactions of the cytokine net also make it very hard to describe single pathways and their outcomes. IL-6 seems to highly correlate with the occurrence of arthralgia but IL-4, IL-10 and TNF-α also contribute to the overall outcome. Despite their inflammatory characteristics, new theories arose suggesting that these proteins could have a great significance in induction of non-inflammatory pain. The pain signal seems to be transduced through the IL-6 receptor and therefore, IL-6 antagonist or inhibitor of its receptor appears as great candidate to effectively attenuate the pathology.

In order to find the optimal treatment, we need to know more about the arthralgia itself. Further research on the selected cytokines must be conducted to elucidate their non-inflammatory, pain signaling properties. Based on that, the mechanism will be better understood and medication can specifically target the major contributors in the arthralgia signaling pathway.

Lastly, it would be convenient to induce the chemotherapy locally so that we can minimize the side effects of whole-system treatment. It would significantly improve the overall outcome if we could optimize and more importantly personalize the cancer treatment. That could be the best way to eliminate unwanted adverse effects and stop the cancer cells from proliferating while allowing for healing processes to occur in the body.

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* stands for secondary citation

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